Journal of Cardiology 66 (2015) 50–56

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

The utility of fully automated real-time three-dimensional echocardiography in the evaluation of left ventricular diastolic function

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ARTICLE INFO

Article history:
Received 10 April 2014
Received in revised form 1 August 2014
Accepted 14 August 2014
Available online 18 September 2014

Keywords:
Diagnosis
Diastolic dysfunction
Echocardiography

ABSTRACT

Background: A novel real-time three-dimensional echocardiography (RT3DE) system allows fully automated quantification of the left ventricular (LV) volume throughout a cardiac cycle. This study aimed to investigate whether an LV time–volume curve, obtained using fully automated RT3DE, is useful in the evaluation of LV diastolic function.

Methods: First, 15 patients underwent simultaneous standard two-dimensional echocardiography (2DE), RT3DE, and cardiac catheterization to measure the time constant of the isovolumic-pressure decline (τ). From the LV time–volume curve obtained using RT3DE, peak early filling rate (PFR) during diastole was generated and indexed for LV end-systolic volume. Next 570 patients, who were scheduled for both 2DE and RT3DE examinations, were enrolled to investigate the association between PFR index and 2DE-evidenced diastolic dysfunction and clinical characteristics.

Results: Of the 585 patients, RT3DE analysis was adequate in 542 patients (feasibility 93%). In the 15 patients, PFR index showed significant correlation with τ ($r = -0.65$, $p = 0.009$). In the remaining 527 patients, PFR index was related to age ($r = -0.24$, $p < 0.001$) and e' ($r = 0.41$, $p < 0.001$). PFR index decreased in proportion to the grade of 2DE-evidenced diastolic dysfunction. All patients with normal diastolic function had a PFR index greater than 2.0.

Conclusions: This study demonstrated that a novel, fully automated RT3DE-derived PFR index was the diagnostic tool of choice for the assessment of LV diastolic function.

Introduction

Left ventricular (LV) diastolic dysfunction is an important determinant of clinical symptoms and outcomes in patients with cardiac diseases [1–3]. The traditional standard approach to characterize diastolic function has involved micromanometric assessment of ventricular pressure decay, i.e. a time constant of the isovolumic-pressure decline (τ) [4], although this method is impractical due to its invasive nature. In clinical practice, several less-invasive imaging techniques, such as radionuclide ventriculography, gated-single-photon emission computed tomography [5–7], and magnetic resonance imaging [8], have been used to obtain global LV time–volume curve and peak early filling rate (PFR), as an index of assessing diastolic physiology. Real-time three-dimensional echocardiography (RT3DE) is a non-invasive tool to obtain 3D information on the LV cavity with acceptable spatial and temporal resolution

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http://dx.doi.org/10.1016/j.jjcc.2014.08.007
0914-5087/

that would be more accurate and physiologic than those measured by conventional imaging techniques [9–14]. A recently introduced RT3DE algorithm enables fully automated detection of the LV cavity surface during a cardiac cycle and acquisition of LV time–volume curve, providing accurate assessment of LV volume and systolic function [15–17]. This study therefore aimed to investigate whether PFR derived from this fully automated RT3DE is useful in the evaluation of LV diastolic function.

Methods

Protocol

This study had two arms: (1) the validation arm included patients who were scheduled for invasive coronary angiography and was used to determine the relation between the variable τ, obtained by direct micromanometric measurement, and PFR index derived from RT3DE; (2) the clinical arm included a relatively large number of patients from four collaborating institutions and was used to determine the relation between PFR index and clinical characteristics, and the results of two-dimensional echocardiography (2DE). The study was approved by the ethics committee in each institution.

Study population

Validation arm

Fifteen consecutive patients (11 men; age, 66 ± 8 years) who were scheduled for diagnostic cardiac catheterization for the evaluation of coronary artery disease were enrolled in the Osaka Ekisaikai Hospital. The exclusion criteria included non-sinus rhythm, history of myocardial infarction, evidence of cardiomyopathy, significant valvular disease (moderate and severe), history of open heart surgery, or presence of other serious systemic diseases. RT3DE and 2DE were performed at the time of cardiac catheterization.

Clinical arm

The clinical arm consisted of 570 patients (413 men; age, 67 ± 12 years) who were scheduled for 2DE examinations. The primary reason for 2DE was coronary artery disease in 401 patients, arrhythmia in 59 patients, hypertension in 53 patients, pulmonary hypertension in 21 patients, and other conditions in 36 patients. Patients were recruited at the following collaborating institutions; 94 patients from the Osaka Ekisaikai Hospital, 49 patients from the University of Tsukuba, 409 patients from the Sakakibara Heart Institute, and 18 patients from the Nishinomiya Watanabe Cardiovascular Center. The exclusion criteria were the same as those in the validation arm. RT3DE images were acquired at the time of 2DE examinations.

Three-dimensional echocardiography

Transthoracic RT3DE was performed using the SC2000 (Siemens, Mountainview, CA, USA) with a 4Z1c transducer (2.8 MHz). A 3D data set including the entire LV was acquired in a single beat during a breath hold. Gain and compression controls as well as settings for time gain compensation were optimized for the quality of 3D images. All 3D data sets were digitally stored and analyzed off-line.

The 3D volume of the LV during a cardiac cycle was analyzed using the SC2000 Workplace (eSie LVA) for visualization and analysis of 3D echocardiographic data (Fig. 1A and B). This software automatically detects the endocardial surface from knowledge gained from large, expert-annotated training databases of volume data combined with a 3D discriminative model, to match relevant image features of the given LV volume to the database [15–17].

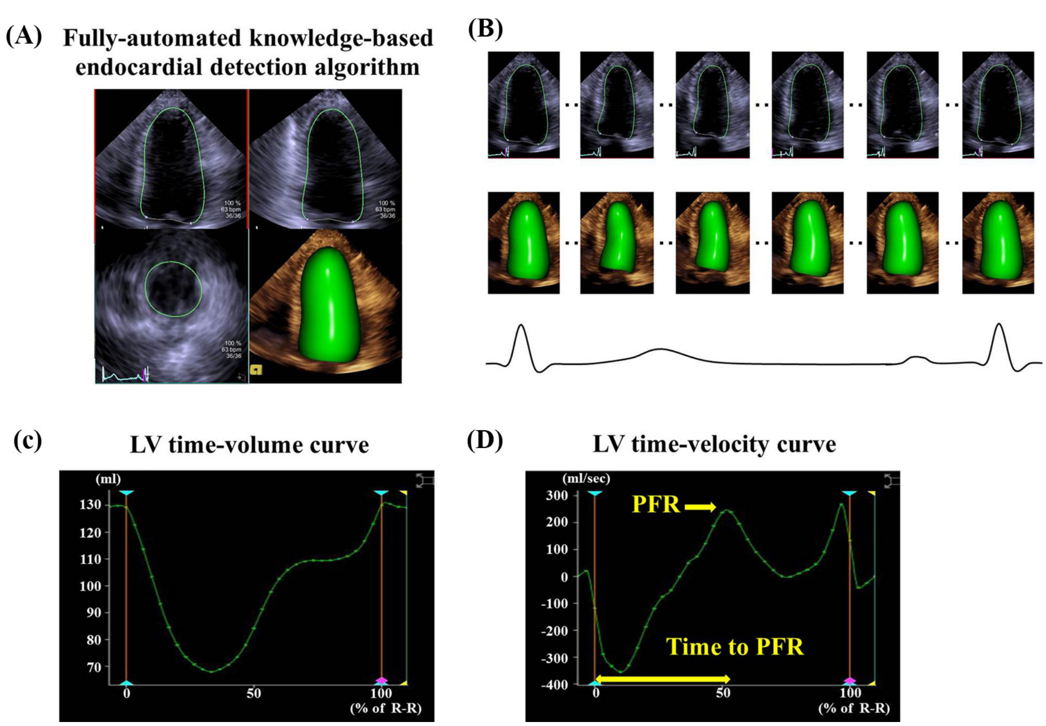

Fig. 1. RT3DE images, showing the process to obtain PFR index. (A and B) The software automatically identified the cavity wall interface in the 3D space throughout a cardiac cycle (green line). (C and D) From LV time–volume curve, LV time–velocity curve was automatically generated. PFR was identified as the first upward peak in diastole. PFR was then indexed to LV end-systolic volume. Time from the R-wave to the point at which PFR occurred was measured. LV, left ventricle; PFR, peak early filling rate; RT3DE, real-time three-dimensional echocardiography. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Time–volume curves were automatically generated for a cardiac cycle (Fig. 1C). Data on end-diastolic and end-systolic volumes and ejection fraction were generated. LV volumes were indexed for body surface area. From the LV time–volume curve, PFR during diastole was obtained (Fig. 1D). PFR was then indexed for LV end-systolic volume. Furthermore, the time between the R-wave and the point at which PFR occurred (time to peak PFR) was estimated and normalized to the R–R interval. Image analysis was defined as successful when approximately >75% of the endocardial border was detected during a cardiac cycle. The RT3DE was analyzed by expert physicians who had >5 years of experience in echocardiography (K.N. and K.O.). They were blinded to all clinical information and the results of 2DE.

Two-dimensional echocardiography

2DE examination was performed using the SC2000 in the standard manner [18]. Left atrial (LA) maximum volume was measured using the Simpson's method from the apical 4- and 2-chamber views, and was indexed for body surface area. Pulsed-wave Doppler examination of mitral inflow was performed to measure early (E) and late peak velocity (A), E/A ratio, and deceleration time of the early diastolic flow. Early diastolic mitral annular velocity (e') was also measured from tissue Doppler imaging in the septal wall. The ratio of E to e' was then calculated (E/e'). Based on the results of LA volume index, E/A ratio, deceleration time, and e', diastolic function was classified into normal, grade 1, grade 2, and grade 3, according to the recommendation of the American Society of Echocardiography and European Association of Echocardiography [19].

Cardiac catheterization

In cardiac catheterization using standard techniques, a high-fidelity micromanometer catheter was advanced into the LV, and both LV pressure and τ were measured. LV end-diastolic pressure was defined as the pressure after atrial contraction, just before the rise in LV systolic pressure. Pressure data were digitized at intervals of 5 ms, and τ was calculated using the method reported by Weiss et al. [4].

Statistical analysis

Categorical variables are presented as frequencies and continuous variables as mean ± SD. The chi-square test was used for comparison of categorical variables. Between-group comparisons were made using the independent-sample t test or Mann–Whitney U test, as appropriate. Linear regression analysis was used for correlation of variables of interest. One way analysis of variance followed by a post hoc Bonferroni test was used to compare the four groups according to the severity of diastolic dysfunction. To evaluate the contribution of the different variables for the PFR index, baseline variables that were considered clinically relevant or that showed a univariate relationship were entered into the multiple linear regression analysis. We examined the relationship between machine settings, such as gain, depth or dynamic range, and RT3DE-derived diastolic parameters in 10 healthy volunteers. As an initial setting, images were acquired with 5 dB of gain, 15 cm of image depth, and 65 dB of dynamic range. Gain, depth and dynamic range were then changed: 0 and 10 dB of gain, 17 and 19 cm of image depth, and 60 and 70 dB of dynamic range. Differences were considered significant at $p < 0.05$. Statistical analyses were performed using JMP 10 software (SAS Institute, Cary, NC, USA).

Results

The RT3DE image quality was adequate for fully automated RT3DE analysis in all 15 patients in the validation arm. In the clinical arm, of 570 patients, 43 patients were excluded because of inadequate detection of the endocardial surface. The feasibility of RT3DE measurement was 93% (542/585). The frame rate of the RT3DE dataset was 27 ± 8 frames per cardiac cycle. Patient characteristics in the validation and clinical arms are summarized in Table 1. Hemodynamics and the results of cardiac catheterization, 2DE, and RT3DE are also shown in Table 2. Of the 542 patients, 369 patients (68%) had e' less than 8 cm/s or E/e' greater than 15, and LV ejection fraction larger than 50%. In these 369 patients, a significant but weak correlation was found between New York Heart Association (NYHA) functional class and PFR index ($r = -0.13$, $p = 0.01$). There were no differences in LV and LA geometries.

The results of the validation arm are depicted in Fig. 2. There was no correlation between τ and PFR ($r = -0.22$, $p = 0.4$), but PFR index (normalized PFR for LV end-systolic volume) was significantly correlated with τ ($r = -0.65$, $p = 0.009$). A similar correlation was observed between τ and e' ($r = -0.52$, $p = 0.04$), whereas PFR index did not correlate with e' ($r = 0.18$, $p = 0.5$). Also, the time to peak PFR was not associated with τ ($r = 0.03$, $p = 0.9$). On the other hand, PFR index ($r = -0.40$, $p = 0.1$) and e' ($r = 0.34$, $p = 0.2$) were not related to LV end-diastolic pressure.

In the clinical arm, PFR index significantly correlated with age ($r = -0.24$, $p < 0.001$), ejection fraction ($r = 0.34$, $p < 0.001$), and e' ($r = 0.41$, $p < 0.001$), as shown in Fig. 3. In the multivariate linear regression analysis, age ($p = 0.03$), male gender ($p < 0.001$), smoking ($p = 0.02$), ejection fraction ($p < 0.001$), and the degree of 2DE-evidenced diastolic dysfunction ($p < 0.001$) were independently associated with PFR index (Table 3). Of the 527 patients, 389 (74%) patients had 2DE-evidenced diastolic dysfunction: grade 1 in 137 patients (35%), grade 2 in 196 patients (50%), and grade 3 in 56 patients (15%). PFR index decreased according to the grade of diastolic dysfunction, although large scatter results were observed in PFR index values, particularly in intermediate values (Fig. 4). The PFR index in normal diastolic patients was significantly higher than

Table 1
Clinical characteristics of the study population.

	Overall ($n = 542$)	Validation arm ($n = 15$)	Clinical arm ($n = 527$)	p value
Age (years)	67 ± 13	66 ± 8	67 ± 13	0.7
Male gender	393 (73%)	11 (73%)	382 (72%)	0.9
Body mass index (kg/m^2)	23.4 ± 3.3	24.1 ± 4.6	23.4 ± 3.3	0.4
Body surface area (m^2)	1.65 ± 0.18	1.62 ± 0.18	1.65 ± 0.18	0.5
Current smoking	124 (23%)	7 (47%)	117 (22%)	0.02
Hypertension	383 (71%)	10 (67%)	373 (71%)	0.7
Diabetes	146 (27%)	10 (67%)	136 (26%)	<0.001
Dyslipidemia	332 (61%)	9 (60%)	323 (61%)	0.9
NYHA functional class	1.5 ± 0.6	2.0 ± 0.6	1.5 ± 0.6	0.01

Values are mean ± SD or n (percentage). NYHA, New York Heart Association.

Table 2
Hemodynamics and the results of cardiac catheterization and echocardiography in the validation and clinical arms.

	Overall	Validation arm	Clinical arm	*p* value
Hemodynamics				
Systolic blood pressure (mmHg)	128 ± 20	136 ± 24	127 ± 20	0.1
Diastolic blood pressure (mmHg)	70 ± 13	68 ± 13	70 ± 13	0.5
Heart rate (bpm)	63 ± 11	71 ± 11	63 ± 11	0.005
Catheterization				
LV end-diastolic pressure (mmHg)	–	8.5 ± 5.2	–	–
LV end-systolic pressure (mmHg)	–	111 ± 19	–	–
Time constant of LV relaxation (ms)	–	48 ± 12	–	–
2DE				
LA volume index (ml/m^2)	25.7 ± 10.1	22.8 ± 7.8	25.8 ± 10.2	0.3
E (cm/s)	63 ± 16	68 ± 24	63 ± 16	0.2
A (cm/s)	75 ± 22	74 ± 15	75 ± 22	0.9
E/*A* ratio	0.92 ± 0.44	0.92 ± 0.29	0.92 ± 0.44	1.0
Deceleration time (ms)	239 ± 56	246 ± 47	239 ± 56	0.7
e' (cm/s)	7.2 ± 2.3	5.8 ± 1.1	7.2 ± 2.3	0.01
E/e'	9.4 ± 3.2	12.1 ± 4.5	9.4 ± 3.3	0.002
RT3DE				
LV end-diastolic volume index (ml/m^2)	57 ± 13	55 ± 17	57 ± 13	0.4
LV end-systolic volume index (ml/m^2)	24 ± 10	23 ± 12	24 ± 10	0.7
LV ejection fraction (%)	61 ± 6	59 ± 10	61 ± 6	0.1
PFR (ml/s)	175 ± 72	145 ± 56	176 ± 72	0.1
PFR index (1 s^{-1})	4.8 ± 2.2	4.3 ± 1.8	4.8 ± 2.2	0.4
Time to peak PFR (%)	51 ± 7	56 ± 7	51 ± 7	0.01

Values are mean ± SD or *n* (percentage). The column showed *p* values for the comparison between validation and clinical arms. 2DE, two-dimensional echocardiography; *A*, late diastolic transmitral flow velocity; *E*, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; LA, left atrium; LV, left ventricle; PFR, peak early filling rate; RT3DE, real-time three-dimensional echocardiography.

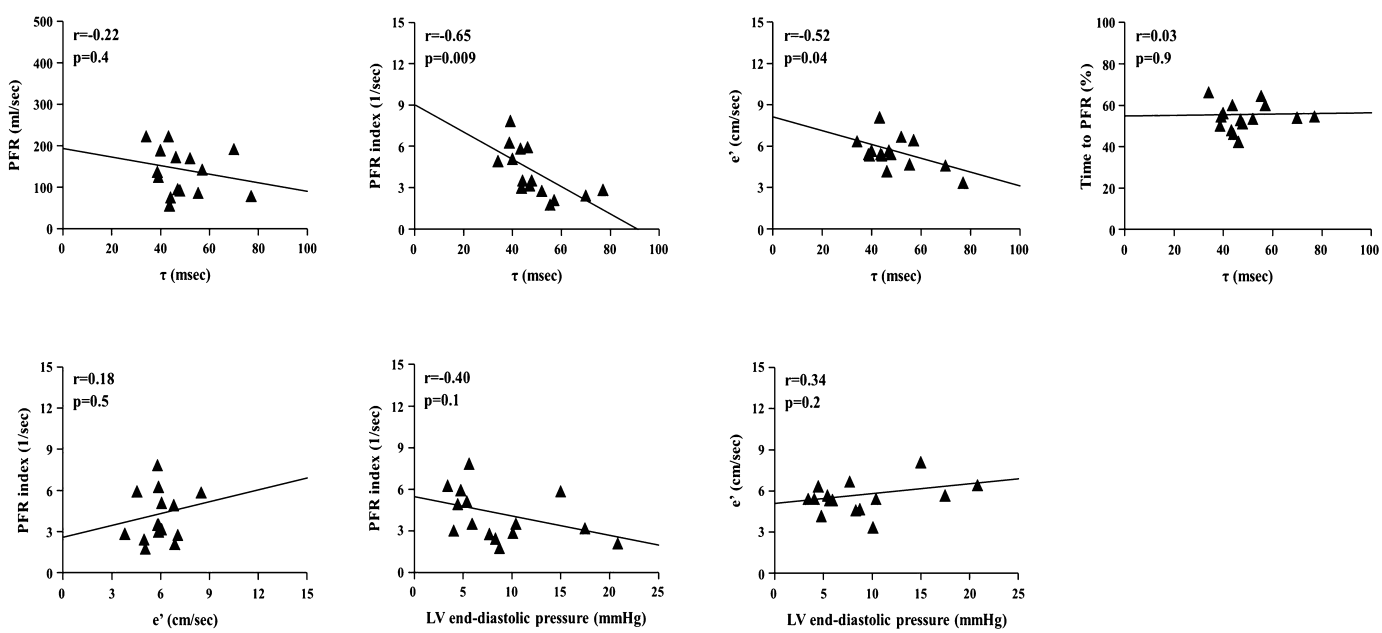

Fig. 2. Scatter plots showing correlations between parameters of cardiac catheterization and those of 2DE and RT3DE. τ, time constant of the isovolumic-pressure decline; 2DE, two-dimensional echocardiography; e', early diastolic mitral annular velocity; LV, left ventricle; PFR, peak early filling rate; RT3DE, real-time three-dimensional echocardiography.

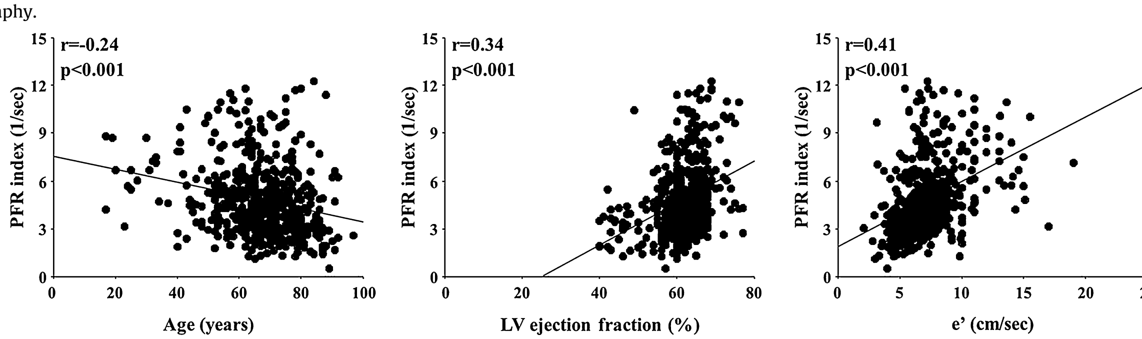

Fig. 3. Regression plots showing correlations between PFR index and age, LV ejection fraction, and e', respectively. e', early diastolic mitral annular velocity; LV, left ventricle; PFR, peak early filling rate.

Table 3
Relationship between PFR index and clinical variables.

	Univariate		Multivariate	
	b (95% CI)	*p* value	*b* (95% CI)	*p* value
Age, years	−0.24 (−0.06 to −0.03)	<0.001	−0.10 (−0.03 to −0.01)	0.03
Male gender	−0.16 (−1.20 to −0.35)	<0.001	−0.15 (−1.15 to −0.37)	<0.001
Smoking	−0.10 (−0.99 to −0.08)	0.02	−0.09 (−0.90 to −0.08)	0.02
Hypertension	−0.22 (−1.48 to −0.66)	<0.001	−0.07 (−0.74 to 0.05)	0.09
Diabetes	−0.04 (−0.64 to 0.24)	0.4	−0.003 (−0.37 to 0.41)	0.9
Dyslipidemia	−0.06 (−0.68 to 0.10)	0.2	−0.001 (−0.35 to 0.36)	1.0
LV ejection fraction	0.34 (0.10 to 0.16)	<0.001	0.27 (0.08 to 0.14)	<0.001
Grade of diastolic dysfunction	−0.34 (−0.96 to −0.59)	<0.001	−0.25 (−0.77 to −0.36)	<0.001

CI, confidence interval; LV, left ventricle; PFR, peak early filling rate.

those of others (all $p < 0.001$). Also, patients with diastolic dysfunction grade 1 had greater PFR index than those with grade 2 ($p < 0.001$). All patients with normal diastolic function had a PFR index greater than 2.0. Representative cases are shown in Fig. 5.

The relationship between machine settings and RT3DE-derived diastolic parameters are summarized in Table 4. There were no significant differences in RT3DE parameters, except for LV ejection fraction and PFR index in response to gain changes. Increased gain setting was significantly associated with higher LV ejection fraction and PFR index.

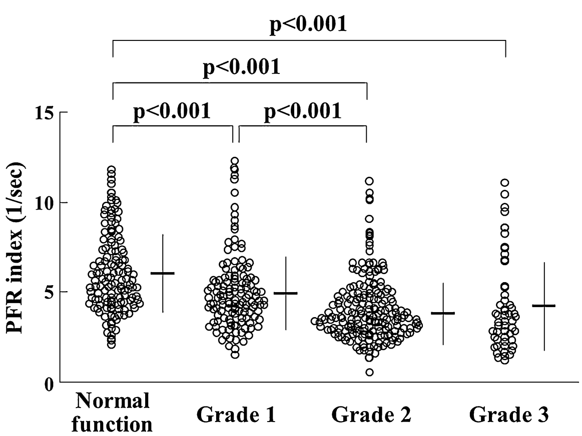

Fig. 4. PFR index in each stage of diastolic function. PFR, peak early filling rate.

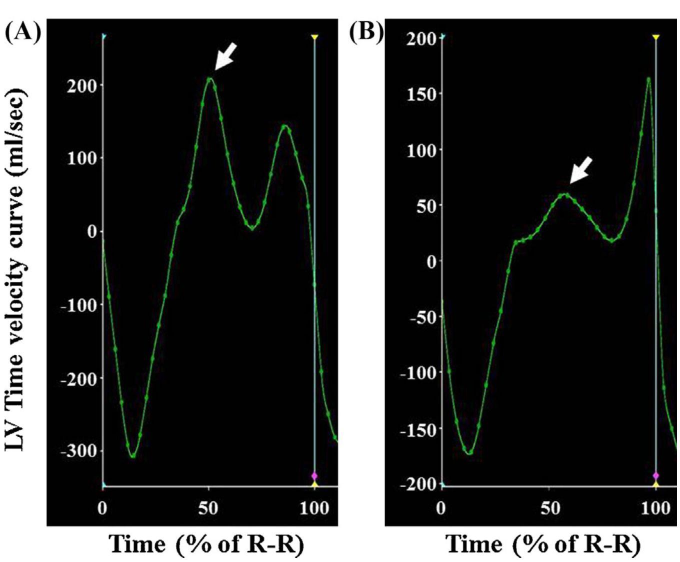

Fig. 5. Representative cases. (A) A 42-year-old male without diastolic dysfunction (e' = 11.0 cm/s, E/e' = 6.1, and LA volume index = 30 ml/m^2) showed preserved PFR index (5.2 s^{-1}). (B) A decreased PFR index (1.9 s^{-1}) was observed in an 81-year-old female with grade 3 diastolic dysfunction (e' = 3.8 cm/s, E/e' = 20.8, and LA volume index = 39 ml/m^2). E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity; LA, left atrium; LV, left ventricle; PFR, peak early filling rate.

Discussion

This study demonstrated that a fully automated RT3DE analysis was feasible to obtain LV time–volume curves in clinical practice (feasibility 93%). RT3DE-derived PFR index correlated with τ and decreased according to the grade of diastolic dysfunction on 2DE. All patients with normal diastolic function had a PFR index greater than 2.0.

Radionuclide ventriculography, gated-single-photon emission computed tomography [5–7], and magnetic resonance imaging [8] have been used to obtain global LV time–volume curve and PFR. However, the utility of these imaging techniques is restricted, especially in sequential or follow-up studies, by their inherent limitations such as high cost, increased time consumption, and radiation exposure (radionuclide imaging only). In contrast, RT3DE permits non-invasive, physiologic, and accurate visualization of the spatial geometry of a given structure and measurement of LV volume. Zeidan et al. [20] showed the ability of traditional RT3DE for measuring PFR in comparison with magnetic resonance imaging. However, cumbersome and time-consuming data analysis precluded the widespread use of traditional RT3DE system for managing patients with cardiac diseases in daily practice. Recent improvements in computer technology have introduced a new RT3DE algorithm that allows automated delineation of the LV surface during a cardiac cycle. Some investigations have validated this novel, fully automated RT3DE to measure LV volumes as well as to evaluate systolic function [15–17].

Another technical advantage of recent RT3DE algorithms is improved temporal resolution. The frame rate of RT3DE dataset (27 ± 8 per cardiac cycle) in this study was comparable to that of previous studies that examined radionuclide imaging and magnetic resonance imaging techniques (approximately 20–30 per cardiac cycle) [5–8]. Consequently, the present study demonstrated for the first time that RT3DE-derived PFR index was associated with τ assessed by cardiac catheterization, and that PFR index decreased in proportion to the grade of diastolic dysfunction. Therefore, PFR index can be used as a marker of LV diastolic function.

Interestingly, PFR index did not correlate with e' in this study, suggesting the possibility that PFR index reflects different aspects of diastolic function based on conventional parameters. The current guideline to assess diastolic function relies on multiple 2DE parameters [19], because each parameter individually has fundamental limitations. For example, mitral inflow is affected by age, mitral valve abnormalities, and left atrial pressure, and may not be reliable in patients with coronary artery disease and hypertrophic cardiomyopathy [21–23].

Table 4
RT3DE parameters with different gain, depth, and dynamic range settings.

	Initial setting	Gain		Depth		Dynamic range	
		0 dB	10 dB	17 cm	19 cm	60 dB	70 dB
LV end-diastolic volume index (ml/m^2)	59 ± 9	64 ± 8	52 ± 7	59 ± 14	57 ± 14	58 ± 8	58 ± 8
LV end-systolic volume index (ml/m^2)	25 ± 10	32 ± 5	19 ± 5	25 ± 11	26 ± 9	26 ± 7	26 ± 8
LV ejection fraction (%)	57 ± 8	50 ± 6*	63 ± 5*	58 ± 7	56 ± 6	56 ± 8	56 ± 7
PFR (ml/s)	274 ± 46	264 ± 39	270 ± 44	259 ± 32	248 ± 45	252 ± 38	266 ± 35
PFR index (s^{-1})	6.6 ± 2.2	4.8 ± 1.0*	8.4 ± 2.6*	6.4 ± 2.0	5.9 ± 1.6	6.1 ± 2.1	6.3 ± 1.6
Time to peak PFR (%)	49 ± 7	52 ± 7	52 ± 7	51 ± 7	49 ± 7	51 ± 6	51 ± 8

Values are mean ± SD. LV, left ventricle; PFR, peak early filling rate; RT3DE, real-time three-dimensional echocardiography.
* $p < 0.05$ vs initial setting.

Furthermore, scattered results were observed in the association between E/e' and LV filling pressure in previous investigations [24,25]. Therefore, ambiguity in the recognition of diastolic dysfunction may arise when these parameters are discordant [26,27]. PFR index may play a complimentary role in patients who show discordant findings in current 2DE parameters for the estimation of diastolic function. Also, PFR index derived from one-beat RT3DE may be useful in patients with atrial fibrillation, because assessment of diastolic function based on multiple 2DE parameters requires multiple beats with similar R–R interval. Patients with a PFR index less than 2.0 can be classified as having diastolic dysfunction.

Study limitations

Several limitations of our study should be mentioned. First, image analysis was defined as successful when approximately >75% of the endocardial border was detected during a cardiac cycle, similar to that reported in previous 2DE studies with automatic detection techniques [28,29]. This visual judgment may require experience in echocardiography. Furthermore, optimal settings, especially gain setting, are of crucial importance for the accurate measurement of PFR index. The RT3DE data were analyzed by expert physicians in this study. Second, because of the fully automated nature, the reproducibility of analysis was 100%. The reproducibility of image acquisition should be examined in future studies. Third, patients' hemodynamic condition in this study was relatively stable because they were recruited in the echocardiographic laboratory. Careful attention may be necessary to extrapolate this result to other situations, such as in the emergency room, because PFR may show "pseudonormalization" in extremely high filling pressure [8,30]. Conventional 2DE assessment should be used as the first-line screening tool [31]. Fourth, the number of patients was small, especially in the validation arm ($n = 15$). Also, τ was not measured in the clinical arm. Thus, the results of this study did not reach the definitive conclusions that PFR derived from RT3DE was superior to conventional Doppler parameters in assessing diastolic function. Finally, the difference in heart rate between the validation and clinical arms may influence the results of PFR value. Other differences in clinical characteristics between the two arms, such as smoking status, diabetes, and NYHA functional class, may cause significant differences in e' and E/e' between the two arms. However, these findings may not affect the results of this study, because RT3DE findings were separately compared to τ or clinical characteristics in each arm.

Conclusions

This study demonstrated that a novel, fully automated RT3DE system allowed for the measurement of PFR index as a parameter of LV diastolic function.

Conflict of interest

There is no conflict of interest and financial disclosure in our manuscript.

Acknowledgments

None.

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